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SACCHAROMYCOTIC TUMOR OF THE CLAVICLE*

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For many years it has been known that yeasts were capable of producing disease. According to Ricketts,[2] Reubold (1854) found yeasts in the respiratory passages and Raum (1891) inoculated yeasts into a rabbit producing death in the animal. Since these writers made their investigations, numerous reports have appeared and pathogenic yeasts are fairly well known. However, very few articles dealing with yeasts as producers of inflammatory change in bone have been published. According to Castellani,[1] Vuillemin and Legrain (1900) reported yeasts as producing a submaxillary bone tumor; Curtis (1896) found yeasts producing a myxomatous tumor and Blanchard and Schwartz found yeast in an abdominal tumor mass of a gelatinous type weighing a kilogram.

CASE HISTORY

A colored male, eighteen years of age, was admitted to the hospital on November 8, 1930 with a complaint of "pain and swelling of right shoulder." In August, 1930, he awoke one morning after a fairly comfortable night's sleep, and noted that he had a slight dull and localized pain in the right shoulder region. In a few days the pain was very severe. Following local applications, the discomforture disappeared leaving a slight swelling. In September and again in November the pain reappeared and he noticed the rapid growth of a tumor mass. During the onset, and following the gradual sequence of above events, he never to his knowledge had chills or fever. There was no history of trauma.

The physical examination revealed a fairly well developed male negro. The pulse beat eighty per minute; the respiration was nineteen; and the blood pressure was normal. In general his appearance was that of a nervous, very weak, and very sick individual. The mucous membranes were very pale. The

* Read before the Tenth Annual Convention of the American Society of Clinical Pathologists, Philadelphia, Pennsylvania. June 7–9. 1931.

pupils reacted to light and accommodation. The teeth were in good condition. The tonsils were enlarged and cryptic. A few glands in the neck were enlarged. The chest was well developed and the excursion was almost normal except for a slight deficiency of the right apex. The bony landmarks were prominent. There was observed an enlargement of the distal extremity of the clavicle. This enlargement was bulb-like, beginning about the middle portion and gradually enlarging as it approached the distal end. In measurement it was approximately 8 by 6 cm. Palpation revealed this tumor mass to be very hard and bonelike, and at no point within the mass was there any softening. Just beneath the middle lower ridge there was a sinus which communicated with the bony structures and from which extruded blood-tinged material.

Within the contiguous tissues, especially posterior to the upper clavicular ridge, there was felt a softened area. Auscultation of the lungs revealed a few râles at the bases. There were also a few râles about the marginal bronchioles. The abdomen and extremities were normal. The laboratory examination revealed a blood count of 12,000 leukocytes per cubic millimeter. Seventy per cent of the white cells were polymorphonuclears. The hemoglobin was 50 per cent. On five occasions Wassermann and Kahn tests were made and in each instance were found to be negative. Smears for tubercle bacilli in the sputum and the sinus exudate were negative. Guinea pig inoculations from each failed to produce tuberculosis.

The roentgenological chest studies revealed a slight peribronchial infiltration. The studies of the clavicle tumor revealed a semi-cystic, semi-solid, productive and destructive change of the acromial part of the clavicle; the walls of the cortex were thinned out, and in two areas there appeared to be sinuses. The radiologist suggested that because of the structure and position and the absence of such changes in other bones, it was very likely that this disease was that of a benign giant cell tumor. This latter opinion was agreed on by two visiting orthopedic surgeons, and he was referred to the radiological department for roentgenologic treatment. The general opinion after a conference was that the disease was neoplastic of a benign type, but some favored the diagnosis of malignant sarcoma. In view of bacteriologic findings medical treatment was advised, based upon the fact that if it were a malignant tumor it had reached such proportions that it was inoperable and if it were benign there was no necessary haste in the matter of treatment.

I administered intravenously sterile solutions of gentian violet at weekly intervals beginning with 20 cc. of 0.5 per cent solution and increasing up to 35 cc. of 1.0 per cent solution. He received eight doses. After each dose the improvement was dramatic and without reactions. By mouth I administered saturated solution of potassium iodide up to sixty drops a day. He was alkalinized and fluids encouraged. On April 15, he was discharged perfectly well. The distal clavicular end was about the same size as that of the left clavicle. The report of the roentgenologist confirmed the curative observations.

BACTERIOLOGICAL STUDIES

A Gram stain and a Wright stain of the draining material each demonstrated the presence of polynuclears, giant cells, fibroblasts, and lymphocytes. Within the giant cells and within the polymorphonuclears were seen many Gram positive yeast-like bodies (fig. 1). There were no other bacteria present. Other smears revealed the same organism. Cultures yielding a yeast were made from material obtained from the draining sinus and also from pus removed by aspiration through penetrating a soft area just posterior to the acromial end of the bone. All cultures were made with the strictest aseptic technic. The media used

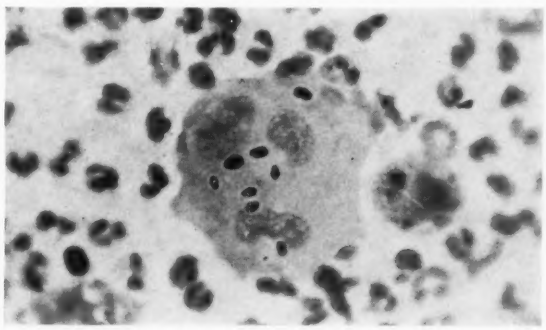

FIG. 1. YEAST PHAGOCYTOSED BY GIANT-CELL

were Sabouraud's, dextrose-beef-bouillon, plain and blood agar. On each of the mediums growths occurred after four days' incubation. The colonies, when very young, were very small and of a white pearly-gray color, turning darker as they grew older. The colony edges were smooth and from mother colonies other colonies were formed in a budding-like manner. The central portions of the growing colony were elevated and dome-shaped. As the colonies became older there was a very definite tendency to marked elevation and bubbles were noted. The colonies exhibited very little granularity but there was a viscid quality and the colonies tended to adhere. In some ways the growing colonies reminded one of a normal secretion from a mucous gland. The organism grew excellently aerobically but did not grow satisfac-

torily when all oxygen was excluded. It grew fairly well when the culture was semi-anaerobic. Satisfactory culture results were obtained on any of the ordinary acid enriched mediums. It did not grow well on plain agar nor upon alkaline material. Slight acid was formed in dextrose and sacchrose and very slight acid in maltose. Gas was never present. Pellicle formation occurred on maltose, dextrose, inosite, inulin and mannite. Litmus milk was unchanged. Gelatin was not liquified. Endo's medium was affected. Mannite agar was definitely resistant. On potato there was a smooth, white, diffuse, elevated colonization. On maltose there was a smooth, white, homogeneous growth. Sabouraud's medium showed a whitish-gray homogeneous growth. An interesting characteristic of the organism was noted when cultures were made upon dextrose-beef-broth-agar; after several days the progressively growing material tended to turn a brownish-yellow color which gradually deepened as it aged. The organism did not produce hemolysis.

CHARACTERISTICS AND LIFE CYCLE OF THE YEAST

In cultures grown on Sabouraud's medium for about a week the organism was observed to be in various stages of division and to be variable in size (fig. 2). They measured in size from 2 to about 30 microns. Unless they were in a state of division, the yeast cells were perfectly rounded and practically all of the smaller ones had within their central portions numerous granular-like bodies. As the cell increased in diameter and approached its largest size, there appeared within the central portion numerous very fine, very small granules which had a Brownian-like movement. At a later stage in the process of development, these dancing granules shifted in an orderly manner toward the periphery of the ectoplasm. As this shift was noted, the movement of the particles within the endoplasm tended to cease its activity and to become quiescent; they were then larger and appeared to be more granular. With this change the large cell appeared to have a cellular structure within a cell in which one portion of the inner ectoplasm had a half-moon shaped appearance. Next came the stage of actual division in which there appeared at some portion of the

capsule an everted nippling. This nippling gradually extended outward until finally it became spherical and detached itself from the parent cell. Occasionally the daughter cell would extend its activity and an adjacent cell would be formed, sometimes three or four daughter cells being formed from one primary cell.

The quiescent cells in very old cultures showed bodies which might be construed as nuclei. In anaerobic cultures which had been growing for a month or more the organism tended to reduce itself in size until it was very, very small, and in this state its characteristic features were represented by a small cell with a rather large, varying-sized nucleus. In anaerobic cultures which had been growing for ten days or two weeks there were observed

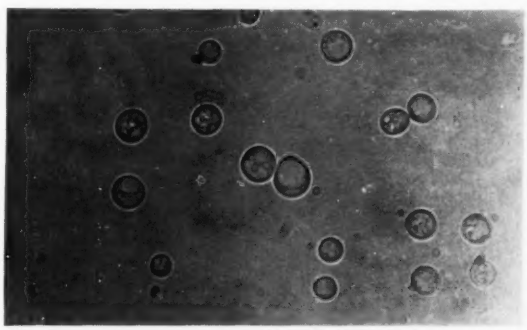

FIG. 2. CULTURE OF *Saccharomyces pyogenes*

very unusual pleomorphic changes, in which these cells tended to change their size and shape, to elongate themselves and to become almost shadow-like and in comparison became shaped very much like sausages. On several occasions I noticed the appearance at the extremity of these forms of a very fine mycelial hair-like process. An attempt to cause mycelia to form by oxygen reduction in the culture was only partially successful. It may be that these yeasts can form a very fine and unusual myceliumIn anaerobic cultures such myceliawere formed and reproduced, yet in the animal I was never positive that it was recovered or that the mycelia played any part in the pathology. I am certain that this yeast does not produce mycelia as is observed in

other pathogenic strains. The observations concerning the possible mycelioid forms in this yeast are important in that they may throw light on the biogenetics of these fungi.

The organism was destroyed after one hour's inactivation at 60°C. Two hours direct sunlight is necessary to destroy it. Agglutinins and precipitins are presumably not formed against it. One per cent phenol kills the organisms. A 1:100 mercurochrome solution, freshly prepared, will also destroy it; above this dilution the organism is unaffected. A half saturated solution of potassium iodide will inhibit the growth of the organism. Seven per cent iodine is an excellent germicide against the yeast. A fresh solution of gentian violet will destroy the organism in dilutions up to 1:31,000 approximately. This latter dye seemingly was the best germicide. Double sub-erythema unfiltered exposures with roentgen rays failed to influence the growth of the organism. The organism is Gram positive. Wright's stain and methylene blue are also excellent staining agents for it.

PATHOLOGICAL OBSERVATIONS

The most outstanding pathological changes in the patient were the very definite anemia, the leukocytic response, and the presence of a tumor mass. It is unfortunate that at first no section was made of the clavicular lesion. It seemed unwise to cut into the bone, fearful of results that might follow if it were a sarcoma. A section was obtained at the time the tumor mass had considerably disappeared, and the sinus had healed. The section showed a chronic inflammatory change in which there were seen a considerable number of fibroblasts of a reparative type, a few giant cells, proliferating bone cells, and a reparative fibrosis. There were one or more small areas where a previous necrosis had evidently existed. It was impossible to say that this tumor had not been a giant-cell type, yet I believe the lesion was purely infectious in nature (fig. 3).

In the animal, pathological observations were more comprehensive. Numerous animals were inoculated with the organism both intravenously and subcutaneously, and into the medullary cavities of bone. Guinea pigs developed hard nodular masses at the

site of inoculation in about three weeks. Incisions into these tumor masses did not show very much necrotic debris, and the inflammatory change seemed to be largely one of a reparatory nature. The organisms were usually present and in every instance were recovered by culture. Sections showed the tumors to be composed of fibrous tissue, leukocytes, lymphocytes, new forming blood vessels, and an occasional giant cell (fig. 4).

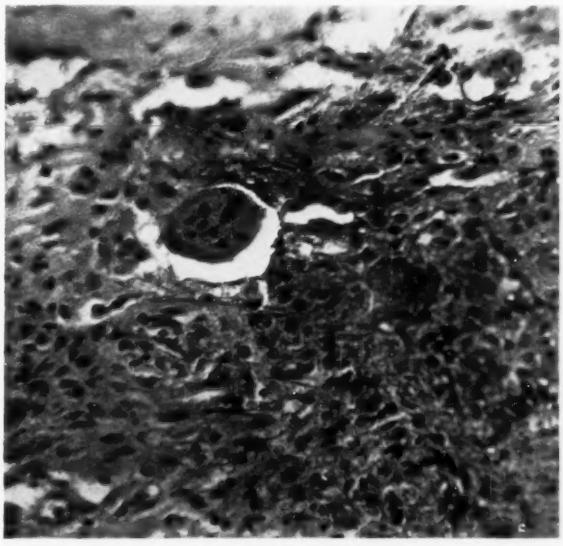

FIG. 3. SECTION FROM TUMOR. NOTE GIANT-CELL

Rabbits inoculated were observed very closely for hematopoietic changes. The rabbits had blood counts made prior to inoculation.

Rabbit 212 was inoculated into the vein on November 24, 1930. Previous to inoculation his leukocyte count was 11,000. Four days later it was 17,000. On December 9, it was 22,600. On December 13, it was 24,800. On the 15th of December it was autopsied. There was a general cloudy swelling and enlargement of the spleen, liver and kidneys. The bladder was tremendously distended and filled with urine. Yeasts were present in the urine.

Rabbit 281 was inoculated December 13, 1930 with a culture of the organism obtained from a previously inoculated guinea pig. The leukocyte count reached

a peak of 20,800, sixteen days after inoculation. It, however, did not show a response until it was reinoculated into the medullary cavity of the left femur on December 22. It developed an abscess in the leg from which the yeasts were recovered. It also became paralyzed on the right side, and at autopsy meningitis was present; the organism was recovered from spinal fluid. This animal is

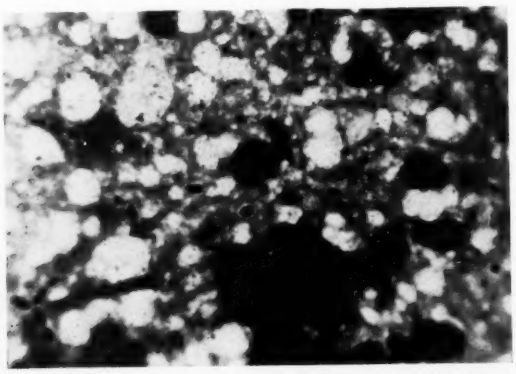

FIG. 4. YEAST IN THE TISSUES OF AN INFECTED GUINEA-PIG

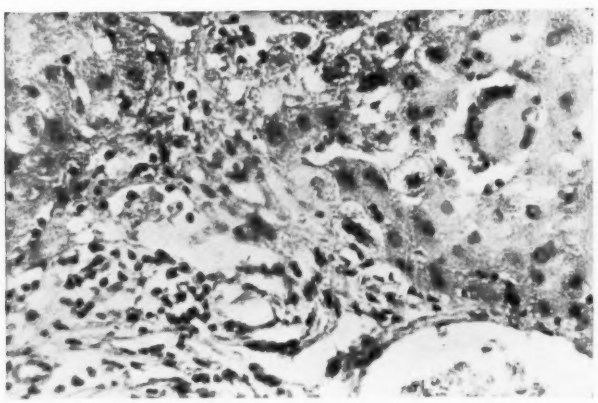

FIG. 5. SECTION FROM INFECTED RABBIT LIVER. NOTE GIANT-CELL

the most interesting of the group inoculated, and since the histological findings are very respresentative of those in the other animals observed, they are given in detail.

The *heart* showed a cloudy swelling of the fibers with a few scattered round cells in between them. There was also a fatty change taking place. The blood vessels were slightly thickened.

The *lungs* were moderately congested. The blood vessels were filled with a coagulable exudate. There were one or two areas which were semi-necrotic.

The *liver* (fig. 5) showed considerable cloudy swelling, a moderate fatty degeneration and thickening of the bile ducts and the arterioles. There was also present a round cell collection about the ducts and the vessels. The most interesting observations was the presence of giant cells scattered throughout the liver substance. They were present in considerable numbers. There were also present a few areas of latent focal necrosis with repair.

The cortex of the *spleen* was thick. The corpuscular areas were hyperplastic. There was a moderate cloudy swelling.

The *kidney* showed cloudy swelling in some areas of the tubules and degenerative changes in others. A few areas were semi-necrotic in type. The glomeruli were shrunken, and some were in a degenerative state; occasionally the arteriole was thrombotic. Casts were also present. Moderate fatty degeneration was also noticed.

The *brain* showed diffuse cloudy swelling with disintegration and atrophy of the ganglion cells. In some areas there were considerable numbers of lymphocytes and polymorphonuclears infiltrating into the brain substance proper. Occasionally a plasma cell was seen. There were also areas that were necrotic. Under the dura there were collected round cells.

The yeasts were positively identified by Gram staining as existing in the tissues of this animal.

Rabbit 216 was inoculated into the medullary cavity and into the blood stream. The left leg was used as control. This rabbit ran a persistent leukocytosis, averaging 20,000. It developed a very definite periostitis which existed from December 9 until March. The animal's leg was definitely enlarged, and the radiological studies showed new bone formation within the cavity. At the time autopsy was performed this tumor mass was receding and nothing can be claimed for more than a very definite inflammatory reaction.

In summarizing the histological features in the animal, the conclusion is reached that the infection is characterized by giant cell proliferation, leukocytic response, cloudy swelling, fatty degeneration, fibrosis and necrosis. Although no tissue is immune, there seems to be a selective affinity for brain substance. A further conclusion is that the organism does not produce acute disease changes in the strict sense of the word, and more often produces chronic and subacute lesions. Even the animals which developed meningitis many days after inoculation did not present symptoms of an acute meningeal involvement. The animals characteristically were paralyzed on one side. As the culture grew older its virulence became lessened.

ARGUMENT FOR ETIOLOGIC INCRIMINATION

The following facts are offered as sufficient to support the claim that this organism was the etiological agent in the disease:

1. The presence of yeasts in the exudate coming from the tumor.
2. The absence of other germs of any type or description, as proved by repeated cultures, anaerobically and aerobically.
3. The presence of the yeasts in the giant-cells and within the polymorphonuclear leukocytes.
4. Recovery of the yeast on fifteen different occasions by culture.
5. The demonstrations of its pathogenicity for animals with the production of a periostitis and other phases of inflammation; the recovery of the organism from the lesions.
6. The serologic observation that the serum of the patient when placed with another individual's leukocytes caused a remarkable ingestion of these yeasts by the leukocytes, although control serum would not give rise to such phagocytic action.
7. The recovery of the patient when treated with chemicals which destroyed the yeasts in vitro.

SUMMARY AND CLASSIFICATION OF THE YEAST

This report is made because of the rarity of such lesions and to suggest particular study of bone tumors of unknown diagnosis and particularly of the benign giant-cell and cystic types. It is within the realm of possibility, and many authorities believe this to be true, that such lesions are due to infectious agents which may respond to treatment more easily given and not so disturbing as surgery. Another reason for the report is to add further evidence of the importance of yeasts as disease producers. The treatment in this instance while radical is seen to be rational and productive of excellent results.

Castellani does not list this yeast. It differs from the pathogens described by Stoddard and Cutter, Blanchard and Schwartz, Vuillemin and Legrain, and by Curtis.

Thus I feel it proper that the new name *Saccharomyces pyogenes* be given it. It should be classified under the Family Saccharo-

mycetaceae and Genus Saccharomyces which contains yeasts not forming typical mycelia.

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STUDIES IN CEREBROSPINAL FLUID. I*

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The cerebrospinal fluid being a product of the choroid plexus, arachnoid, et cetera, structures intimately related to the central nervous system, both morphologically and physiologically, may naturally be expected to reflect in its properties pathological involvements of this system. An examination of the cerebral fluid has thus become a routine procedure in the clinical diagnosis of many conditions, and numerous procedures have been developed, aiming to detect and differentiate the various changes that take place in certain diseases of the nervous system. With the exception of the Wassermann test, which is based on a reaction specific for syphilis most of the other tests are chemical or physical, depending on the difference in concentration of some constituents of the fluid in normal and pathological conditions. An examination of the actual differences in chemical composition between cerebrospinal fluid from normal and pathological individuals, however, shows a distinct and definite change of any magnitude to occur in regard to only one colloidal compound, namely, protein. Nor is this very surprising when the nature of the fluid is considered. It contains normally very little protein, and contains salts in concentrations related to the composition of the blood, most probably according to the simple physicochemical laws of distribution across a membrane. It is to be expected, therefore, that any condition involving the meninges or other sources of spinal fluid should affect its protein content, regardless of whether its formation is considered to be one of simple filtration, secretion, or excretion. The composition of other constitu-

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ents will also naturally change, but not in so marked a manner as that of the proteins, as analysis has demonstrated. Examination of the methods that have been suggested for examination of pathological fluids, will show that they depend on the increase in the protein content of the fluid. Thus the foam test described by Levinson is dependent on a high content of protein. The various precipitation tests, the colloidal gold reaction of Lange, the mastic test of Emmanŭel, are all probably dependent on a high protein content of the fluid for their value as diagnostic agents. The same is true of Pandy's, Ross-Jones' and Noguchi's tests, all of which are protein tests.

Of all these methods, the Lange test stands out as the most valuable diagnostic procedure, but it suffers the disadvantages of being cumbersome, of requiring a rather elaborate technique and scrupulous care in its use and of being easily invalidated. This paper describes a simple test which depends on the protein content of the spinal fluid and which being of extreme simplicity in regard to ease and rapidity of manipulation can act as a useful means for the laboratory diagnosis of abnormalities in the spinal fluid.

PROCEDURE

Ten Wassermann tubes are set up in a rack. Into tube 1 there is pipetted 0.3 cc. of spinal fluid, into tube 2 there is pipetted 0.23 cc. of spinal fluid. To tube 1 there is added 0.7 cc. of physiological saline, and to tube 2 is added 0.77 cc. of saline, bringing the volume in each tube up to 1.0 cc. Into each of the other eight tubes 0.5 cc. of saline is added. The fluid in tube 1 is well mixed, by gently shaking or by pipetting, and 0.5 cc. is transferred to tube 3, mixing well and transferring 0.5 cc. to tube 5, and so on in alternate tubes until the ninth tube is reached, from this tube 0.5 cc. is discarded. Then beginning with tube 2, the fluid is well mixed and transferred similarly in series to tubes 4, 6, 8, 10, discarding the 0.5 cc. from tube 10.

To each tube is then added 1.0 cc. of starch-iodine solution. The tubes are carefully agitated until the color is uniform in each tube, and the color of each tube is read immediately. The final readings are taken one-half hour later.

The starch-iodine solution is made as follows:

One part aqueous iodine (0.1 gram in 1000 cc. distilled water).
One part starch solution (0.75 gram in 100 cc. of saline).
One part physiological saline (8.5 grams NaCl in 1000 cc. of distilled water).

One-tenth gram of fine iodine crystals will dissolve in the water in from three to four weeks. The water must be absolutely free from organic matter so that the solution of iodine will not be weakened by any reaction or standing. Soluble starch is used for the starch solution and is heated only until a clear solution is obtained. The solution need not be boiled and should not be used when it has become cloudy on standing. The glassware for the test should be chemically clean and dried by sterilizing in the gas oven, thus keeping it free from foreign matter, such as lint, dust and the like.

The readings are made in symbols as follows: decolorized tube, O; light blue color, L; standard blue of starch-iodine solution, B. Enclosing the letter in parentheses indicates a lesser value, thus, (L) indicates a very pale blue color and (B) a slightly affected affected standard blue color.

In normal fluid two tubes are slightly affected, and one tube is sometimes decolorized.

In tabes, from four to five tubes are affected and two of these are decolorized.

In paresis, from five to six tubes are affected and three of these are decolorized.

In meningitis, from seven to nine tubes may be effected, according to the severity of the case and from five to six of these are decolorized.

It is interesting to note that if there is a clinically appreciable improvement in treated cases of meningitis, paresis, or tabes, the same number of tubes is affected, so that as long as the condition prevails the same number of tubes is decolorized, but to a lesser degree, the colors in the tubes being fainter than in the untreated cases. This characteristic has been especially noticed in cases of meningitis.

It has been observed that when a pellicle, or coagulum has formed in a spinal fluid the reaction does not attack the usual number of tubes, but that a curve is obtained in which two tubes less than the usual or typical number are decolorized. That this condition also affects the colloidal gold readings is shown in the table which gives comparisons between the typical Lange colloidal gold and the Gruskin tests. In the formation of the pellicle, it would seem that a considerable amount of the proteins are held together and thus kept from entering into the reactions.

In nearly 200 spinal fluid tests, the results have checked with the Lange colloidal gold test in all but one, which was a case of treated syphilis, in which the Gruskin test did not coincide with the Lange. The tabulation gives a few of the results in order to show the various types of curves obtained with the test.

COMPARISON BETWEEN LANGE AND GRUSKIN TESTS
(Typical tests)

DIAGNOSIS	LANGE	GRUSKIN
Normal	01000000000	(B)BBBBBBBBB
	01100000000	L(B)(B)BBBBBBB
Tabes	12222211110	OOLL(B)BBBBB
	11124432100	OOL(B)BBBBBB
Paresis	5555544100	OOO(L)(B)BBBBB
	5555555321	OOOL(B)BBBBB
Meningitis	11111343210	OOOOOOL(B)(B)B
	12222333210	OOOOL(B)BBBB

THEORETICAL CONSIDERATIONS

The theoretical basis of the test is dependent on the behavior of colloial proteins in solution. There are several theories concerning protein behavior each of which have logical arguments in their support, but none of which as yet has been unanimously accepted or established in stoichiometrical form.

Thomas Graham was a pioneer in the study of the visibly amorphous state of matter which he suggested calling colloidal, as opposed to matter with a definite crystalloidal structure. Also he was the first to suggest the possibility of the same substance occurring in both the colloidal and crystalloidal states. He[3] wrote "The inquiry suggests itself whether the colloidal molecule may not be constituted by the grouping together of a number of smaller crystalloidal molecules, and whether the basis of colloidality may not really be due to this composite character of the protein, or other colloidal molecule." Modern research has fixed the dispersion into particles between 100 and 5 $\mu\mu$ as the

criterion of the colloidal condition, and the particles may be crystalline or consist of random clusters. But these statements of Graham still hold true.[6] If this suggestion were so, the logical consequence would be that colloids should be governed by laws analogous to those of the crystalloidal systems. This has been lost sight of for a considerable time and it is only recently that the analogy has been again under consideration.

Grolman, working with phenolsulphonephthalein, claimed that the substance was taken up by serums and aqueous solutions of varying amounts of proteins, according to the Freundlich isotherm

$$\frac{x}{M} = \alpha C \frac{1}{n}$$

where x is the weight of substance adsorbed by M, the weight of the adsorbent, C is the volume concentration at equilibrium, and α and $\frac{1}{n}$ are constants varying only over a wide range. Loeb[5] attempted to refute this theory on the charge that the observers did not consider the pH of the protein solutions under consideration, thus obtaining inconsistent results with the variation in pH. Loeb adhered to the chemical view that proteins form true ionizable salts, for example, gelatine chloride and sodium gelatinate. On the other hand, Loeb's theories have been contested on the ground that he did not demonstrate protein, namely, the gelatine used by him, as a definite chemical entity, and that he was not sufficiently specific as to quality and composition. Robertson[6] has drawn the following comparison: our knowledge of the colloidal character of proteins, especially concerning their indiffusibility or slight diffusibility, has created the impression that in solution they will furnish surfaces at which adsorption may occur. It is inferred and granted that the ultimate particles of protein in solution are very large in comparison with molecules of crystalloidal substance; from this the conclusion is drawn that such large particles would present a surface to the surrounding medium at which adsorption might occur. But, he adds, if the chemical constitution of the proteins is considered, it is quite

evident that the ultimate chemical unit of protein, the molecule itself must be very large. As an example, the proportion of iron in hemoglobin indicates a molecular weight of 16,000, that of tryosine, glutamic acid, and cystine in casein indicates a molecular weight of from 4000 to 4400; phenylalanine in gelatine indicates a weight of 11,800. Thus it is evident that the colloidal properties of proteins must naturally follow from the magnitude of their molecules. Therefore the ultimate surface which separates the protein from the solution must be the molecular surface in the protein as well as in other substances, for it has been demonstrated that in nearly all instances single or double molecules serve to account for the colloidal behavior of protein solutions. Therefore since adsorption at the surface of the molecule of sodium chloride, water or sugar is not spoken of, why should this be attributed to the protein molecule alone. If adsorption did exist at the molecular surface would it be distinguishable from chemical combination? Then should the same phenomenon be called chemical combination when it involves a small molecule and adsorption when it involves a large one? On the other hand, in a recent study Field[2] claims that the significance of dilution as a factor in determining the iodine binding capacity of starches suggests that starch-iodide is an adsorption compound. A lack of specificity towards the combination with iodine shown by the various starches also seems to point towards adsorption.

At any rate it is now admitted by all observers that the proteins accomplish the neutralization of acids and bases in stoichiometrical, that is molecular or equivalent molecular, proportions.[6] Many refuse to admit a purely chemical mechanism and invoke a physical mechanism, that is, molecular attraction between the colloidal particles of protein and the molecules of acid or base which are neutralized.

In the reaction of the blue starch-iodide mixture with the proteins of the spinal fluid, the sensitiveness of the test is dependent on the affect of the proteins on the iodine, the starch serving the purpose of forming the blue complex but evidently not reacting with the proteins themselves. This is demonstrated in positive cases of reaction where the color is discharged, for

an addition of starch does not renew the color, whereas introduction of a sufficient amount of iodine does again produce a blue color. Inorganic constituents had a negligible effect on the reaction so that it is a specific test for proteins. It has been pointed out by Chesley[1] that starches from different makers give different results in their digestibility with enzymes, as tested with the iodine reaction. It is therefore advisable to avoid variation in readings of this test that the starch of one company be used constantly. In this manner any inaccuracies from the use of starches of different values will be eliminated.

Regarding the sensitiveness of the test, it is well to note that procedures involving the starch-iodide reaction offer possibility of great delicacy, inasmuch as by this reaction it is possible to detect as little as 0.0000001 grams of iodine per cubic centimeter of solution.[4]

SUMMARY

A simple colorimetric diagnostic test for spinal fluid has been described. Only a small amount of fluid is required. The procedure is devoid of the usual difficulties of the other tests, and since it is based on a sound theoretical mechanism, it is hoped to have a diagnostic value in the routine examination of the cerebral fluid superior to many of the more complicated tests in use at present.

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THE THERAPEUTIC USE OF BACTERIOPHAGE AND ITS PRACTICAL DIFFICULTIES*

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The mechanism of bacterial lysis is still so little understood that no one can state dogmatically what bacteriophage is. For the purpose of this brief discussion bacteriophage may be defined as that principle which brings about transmissible lysis of bacteria; bacteriophage also increases or multiples during that process. It is not necessary to go into the question of whether bacteriophage is a virus, an enzyme, or a product of autolysis. It has properties suggestive of each of these. Most of the facts known concerning bacteriophage would apply to a virus, and this explanation is more easily comprehended than the explanation of the phenomenon upon purely physico-chemical grounds.

Whatever shall finally be found to be the true nature of bacteriophage, it certainly has not been decided at the present time, and it is not within the province of this review to try to settle it. It is my purpose to point out the principles underlying bacteriophage therapy, and some of the causes of failure of this form of treatment.

The lysis of a culture in vitro by specific bacteriophage is so spectacular, that we were justified in our hopes and expectations that the same thing would take place in the animal body harboring pathogenic organisms.

Experimental studies have indicated that the course of an experimentally induced infection can be favorably influenced by a bacteriophage capable of lysing the causative organism.

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The results of the clinical studies have possibly been a little more optimistically interpreted than have the experimental data, as it is quite impossible to subject clinical studies to the same rigorous methods as are applied to experimental work.

The infections in which bacteriophage is of value are, as a rule, those in which the infectious process is largely on or near the surface. For example, the most brilliant results reported from this method of treatment are in cholera. The results reported by d'Herelle[1] in this disease are more spectacular than those reported by others in any condition.

There is practically a unanimity of opinion of those reporting upon the use of bacteriophage in the treatment of staphylococcic infections, that the method is of value. This was brought out by Larkum[2] in an analysis of some 700 reported cases. It is possibly a mistake to try to evaluate the results of bacteriophage in all types of staphylococcic infections grouped together, because of the great variety of lesions present. The accessibility of the staphylococci in an open wound infection, for example, is quite different from that in an abscess, a paranasal sinusitis or an osteomyelitis.

This is probably the principal cause for failure in treatment of staphylococcic infections. The accessible staphylococci can be readily lysed by bacteriophage, and with less tendency to secondary growth than is the case with most organisms. This is apparent in the treatment of staphylococcic wound infections, which are usually benefited by bacteriophage therapy.

The following case brings out a point of considerable importance.

The patient had had an amputation below the knee. The stump became infected with *Staphylococcus aureus*, and after other measures had failed the wound was treated with staphylococcic bacteriophage. Improvement was immediate but when the treatment was changed to a mixed commercial preparation of colon-staphylococcus phage, a secondary infection with *Pseudomonas aeruginosa* (*B. pyocyaneus*) occurred. On subsequent examination it was found that the mixed phage was contaminated with live organisms. These broth filtrates are perfectly satisfactory for the growth of heterologous organisms, and great care should be exercised to prevent their contamination, not only during preparation but also at the time of applying.

In typhoid fever and dysentery, bacteriophage therapy has apparently been unsatisfactory. I have had little experience with it in typhoid fever, and none in dysentery.

In the colon bacillus infections the results have been very variable. Some of the reports of bacteriophage treatment of pyelitis have been favorable, but many of them have indicated little or no effect. I have seen one case of pyelitis in a young girl in which the result was very gratifying, but for the most part the results in this condition have so far been only fair. The best results in infections due to the colon bacillus have been in those of abdominal wounds.

Pelouze and Schofield[3] reported the development of a bacteriophage in lysed cultures of gonococci, but this substance was without therapeutic effect in gonococcic infections. Bacteriophages have been encountered that were effective against most of the common infectious organisms in the test tube, but most of these have been ineffective in the body.

Several factors are responsible for the variability in the therapeutic effect of bacteriophage. First, as mentioned above, the accessibility of the pathological focus to the bacteriophage filtrate, is of primary importance.

Second, if a bacteriophage does not completely destroy a culture, the organisms that survive give rise to a resistant strain of organisms. These may still be pathogenic for the host but unaffected by the bacteriophage. There is available for staphylococcic infections a bacteriophage which is lytic for practically all strains of staphylococci, and is so potent as to destroy many strains without the development of resistant forms. Colon, typhoid, and dysentery bacilli, on the other hand, develop resistant strains much more readily. Only young cultures of most strains of these organisms are susceptible to complete lysis, and the older organisms become the progenitors of resistant strains.

Third, bacteriophage is not very effective against blood borne infections, because of the adsorption of the phage by the colloids of the serum. In some manner not well understood the bacteriophage sometimes becomes free from the colloid and localizes at the site of infection. It would be difficult to explain on any other

basis the fact that bacteriophage is to some degree effective, in experimental animals at least, when injected at a site distant from the infective focus.

Fourth, it has been found[4] in certain experimental infections, as in peritonitis for instance, that to get the effect of bacteriophage, it must be injected before or within a half hour after the bacterial inoculation. This condition cannot be fulfilled in clinical practice, and in such infections the use of bacteriophage will have to be limited to prophylaxis for the present. Some experimental data encourage us to hope that the prophylactic use of bacteriophage may prove of some value in these conditions.

Finally, the protein present in a bacteriophage filtrate has an important bearing on the dosage and method of choice for administration. The protein is derived, from the extractives in the culture mediums, and from the bacterial protein of the lysed organisms. When bacteriophage is to be administered by mouth, as in cholera, typhoid fever, dysentery, et cetera, the protein present in a dose of 2 to 10 cc. is of no significance, but if it is to be injected intravenously the amount of peptone and bacterial protein in the filtrate becomes a matter of major importance. To a lesser extent this is also true of subcutaneous or intramuscular administration. I have seen a very severe and extensive local reaction follow a dose of what evidently was a too highly concentrated bacterial protein.

Bacteriophage may be administered by mouth, by irrigation, by wet dressing or by inoculation. The administration by mouth is the method of choice in cholera, typhoid, dysentery, et cetera. I have administered it by mouth in pyelitis also, in the hope that some of the phage might be excreted by the kidney. When bacteriophage is given by mouth it does not cause the development of an antibacteriophage which is a decided advantage. From 2 to 5 cc. of an active phage filtrate may be given daily over a period of from seven to ten days.

Wet dressings of bacteriophage sometimes have a spectacular effect on wound infections. I have seen this both in staphylococcic and in colon bacillus infections. Bacteriophage usually from 1 to 4 cc., is poured into the wound, and a wet dressing of physiological salt solution is applied.

Probably the commonest method of administration of bacteriophage is by subcutaneous inoculation. This may be given intramuscularly or intravenously. The latter method is seldom used because of the adsorption of bacteriophage by the colloids of the blood, as mentioned before. The filtrate is usually injected directly into the lesion, but at least in certain experimental infections, it may act on a distant focus. This was shown by Walker[4] in peritonitis in mice. Bacteriophage may be injected directly into and around a boil or carbuncle. The dose varies from 0.1 to 1.0 cc. according to circumstances. In pyelitis the method of choice is irrigation of the bladder, and possibly the pelvis of the kidney.

It would be desirable to have a more definite method of standardization of bacteriophage filtrates. Various authors have specified their dosage simply according to the quantity of filtrate used, or by the number of phage corpuscles in a dose, or by the number of lysed organisms in a dose.

For the present it is probably best to designate the number of corpuscles in each cubic centimeter of filtrate, and adopt some arbitrary number, as a billion in each cubic centimeter, as a unit.

When more is known of the chemistry and antigenic properties of these filtrates of lysed organisms, it may be found that a large part of their therapeutic or prophylactic value is due to the bacterial protein, and that standardization on the basis of the number of lysed organisms is more logical than the present method.

Bacteriophage filtrates have failed to justify our hopes that they would prove a panacea for infectious diseases, but there is reason to believe that they have a definite place as valuable therapeutic agents.

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THE NATURE OF HODGKIN'S DISEASE

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The origin of Hodgkin's disease has always been confusing. We shall attempt to show that the disease is probably neoplastic and that it belongs to the group of lymphoblastoma.

A variety of names has been applied to this condition, such as multiple lymphadenoma, lymphogranuloma, lymphoblastoma, lymphocytoma, malignant granuloma, infectious granuloma, lymphosarcoma, and pseudoleukemia. Mallory,[9] and MacCarty[8] each suggested that all these terms be grouped under the heading of lymphoblastoma, which would indicate any tumor composed of cells of the lymphocytic series. This group would also include all forms of lymphatic leukemia. Warthin[15] selected the name lymphocytoma to designate all hyperplastic tumors and those that resemble neoplasms of the lymph nodes, depending on an overgrowth of cells of the type of small or large lymphocytes.

Ewing[3] stated that a consideration of lymphomas should include the various processes by which they are produced, for some of them are inflammatory, some neoplastic, and others intermediate in position. Lack of knowledge of the etiologic factors and of the intricate relation of many forms of lymphoid hyperplasia, and the occasional transformation of one form to another, makes a classification on an anatomic basis justifiable. Even in this difficulties are encountered because the relation of the lymphocytes and the reticulum cells has not been definitely determined, and the distinction between sinus cells, endothelial cells, and reticular cells is not definite.

Thomas Hodgkin,[6] in 1832, described a clinical syndrome in which there was swelling of the lymph nodes, which syndrome was designated by Wilks as Hodgkin's disease. In the following years

many terms, as mentioned previously, were applied to this condition. Until Sternberg[12] described it as a peculiar form of tuberculosis, most investigators looked on the disease as a neoplastic condition. Reed[10] then gave an accurate description of the lesion, which has changed the status of the condition from that of a clinical syndrome to that of a pathologic entity. However, since that time, numerous articles have been written dealing with various phases of the malady, but not a single conclusion has been reached regarding its true nature. There is still much disagreement as to whether the lesion is a neoplasm or a granuloma resulting from an inflammatory process.

Tuberculosis as a probable excitant has been widely commented on. Sternberg at first emphatically maintained that Hodgkin's disease was of the same etiology as tuberculosis. Later he modified his position and admitted the existence of nontuberculous forms. Fraenkel and Much[5] demonstrated Gram-positive bacilli and acid-fast granular bacilli in twelve of thirteen cases of Hodgkin's disease, and suggested that these were certain forms of organisms of tuberculosis. Ziegler[16] also pointed out that the condition in 20 per cent of the cases was associated with tuberculosis and that in 10 per cent the reactions to inoculation were positive.

Sticker[13] reported that the bovine type of the organism of tuberculosis was found in the lymph nodes after repeated passage through guinea pigs. L'Esperance[7] inoculated chickens with emulsions from the lymph nodes and typical or atypical tuberculosis developed in all; inoculation of other chickens resulted in even more extensive manifestations of the disease. She concluded that the avian type of bacilli might be important in the production of Hodgkin's disease.

Sweany[14], stated that the disease pursues the typical course of an infectious condition, and that the organism of tuberculosis might degenerate and pass over into the diphtheroid type that was practically a distinct species; he stated that he had been able to produce such forms. He also stated as his belief that tuberculosis of the lymph nodes often developed into Hodgkin's disease, and that the whole picture was a heterogeneous degeneration of an

atypical strain of organisms of tuberculosis in a particular type of host that had failed to overcome the parasite.

Stahr[11] expressed himself in favor of the view that the lesion was of the nature of a tumor with organisms of tuberculosis as an excitant. He stated that for the production of a tumor the stimulus must not be strong enough to break down the defensive forces of the body. The inflammation need not be specific, but it was essential that the irritation be mild and of long duration. He stated as his belief that when the defensive efforts of the body were not aroused, enormous hyperplasia might be present.

Syphilis has never been seriously considered as a cause of Hodgkin's disease, but it has been mentioned by Fabian[4] and other older observers. However, a positive Wassermann reaction has never been obtained except in cases in which syphilis was present independently.

It can readily be seen how difficult it is to apply any definite designation or classification until the etiology of this group of conditions becomes known. Staining of sections for the organism of tuberculosis has failed to reveal it, but in one case tuberculosis was associated. Tuberculosis with hyperplasia and without caseation, sometimes simulates Hodgkin's disease. The fact that the node filters lymph makes it most commonly involved secondarily, and it is very difficult to determine whether one is dealing with a neoplasm or a granuloma. In the intermediate types it is even more difficult to determine whether the process is strictly inflammatory or neoplastic. Productive inflammation usually involves all the elements of the node, whereas a neoplastic process usually involves a single cell type; yet is should be remembered that in the same person hyperplasia may remain simple in one situation, but take on neoplastic properties in another situation and that infection may play a part similar to the one it plays in carcinoma. Theoretically there may be a point at which the transition occurs between inflammatory hyperplasia and neoplastic hyperplasia. Thus it may be seen that the numerous types of lymphoma described may be different stages or manifestations of the same disease.

The material used for this study consisted of 200 cases of Hodg-

kin's disease in which one or more cervical lymph nodes were removed as a part of treatment or for diagnosis. All of these cases were observed and the patients were treated at The Mayo Clinic between 1910 and 1920 and they have been traced and their subsequent condition noted. In this series the youngest patient was a boy aged four years, and the oldest patient, a man aged sixty-five years. The duration of the disease was from six months to seventeen years, with an average of two and sixty-five hundredths years. The disease occurred much more frequently in males. The response to roentgen therapy was practically the same as that of lymphosarcoma.[2]

The nodes were usually enlarged, and sometimes measured 4 cm. in diameter. They might be round, oval, or oblong, and might have a distinct capsule, which was frequently thickened. The nodes, in an involved group of nodes, were discrete. On gross examination the fresh specimen was salmon-pink, homogeneous, and had a consistence resembling rubber. Its appearance was sometimes altered by the duration of the condition, degenerative changes, and previous treatment. In the nodes that grew very rapidly, or that were most malignant there might be some central necrosis. Those that grew more slowly contained more fibrous and hyaline tissue, thus altering their color and consistence. Previous roentgen therapy might also produce similar changes. The capsule was rarely, if ever, invaded by the neoplastic process. On microscopic examination, the nodes in different cases varied in appearance, depending on the degree of malignancy present.[1]

The disease began in the so-called germinal centers, the cells of which are derived from the wandering histiocyte which in turn is derived from the fixed histiocyte, or what might be called the stem or parent cell. Thus, Hodgkin's disease and lymphosarcoma are derived from the same stem cell, but differ in the degree to which this cell becomes differentiated. The second parent cell of Hodgkin's disease is the free or wandering histiocyte, whereas the second parent cell of lymphosarcoma is the lymphoblast. It would be possible for the two conditions to be associated.

In the first stage there was extensive catarrhal inflammation of

the sinuses in the form of hyperplasia of the lymphoid cells, with active proliferation of the germinal centers. Vascularity was also increased. The sinuses were dilated and contained small and large lymphocytes, polymorphonuclear leukocytes and eosinophils. In the reticuloendothelial cells, mitotic figures might be found. The reticulum was prominent, and large lymphocytes,

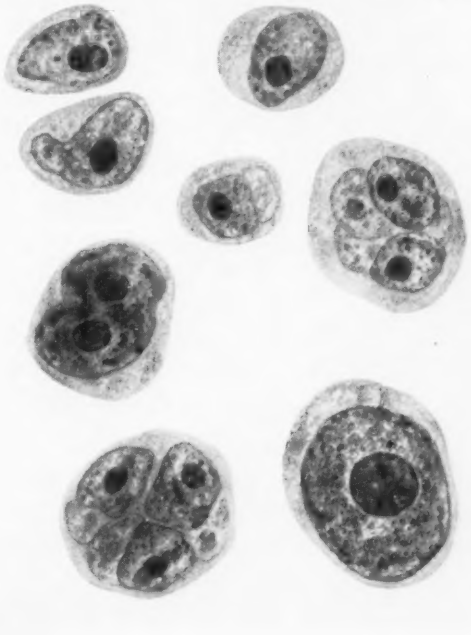

FIG. 1. SINGLE AND MULTINUCLEATED CELLS CHARACTERISTIC OF HODGKIN'S DISEASE. DRAWINGS FROM PHOTOGRAPH. (×1100)

epithelioid cells, plasma cells, mast cells, and eosinophils were often distributed profusely.

In the second stage the appearance was more striking. The thickening of the reticulum became more noticeable. A coherent tissue appeared which was formed of large cells, with elongated, vesicular, and rather palely staining nuclei. The cells lay in no particular order, and with other lymphoid cells soon spread to

replace the normal tissue, and to obliterate the distinction between lymph cords and sinuses. Here and there the remains of lymph follicles might be seen. The capsules were thickened, but distinct, narrow bands of connective tissue divided the node into irregular lobules, and fibroblastic proliferation became more prominent.

The multinucleated giant cells formed a fairly constant picture. They were probably formed by the unicellular giant cells which in turn are derived from the reticular endothelium. The uninuclear giant cell was very irregular in form, and had a clear protoplasm, containing a large nucleus, which might be multilobular and might contain one or more nucleoli. Surrounding the nucleus was a fine, deeply staining portion of chromatin, and in the center, a well defined network, with one or several deeply staining and sharply defined nucleoli. The nuclei numbered from 4 to 10, and were heaped together in the center of the cell. Occasionally there was a second form in which the nuclei were shaped in the form of a horseshoe around the periphery of the cell. This type resembled closely the Langhans giant cell of tuberculosis. The nuclei resembled those found in foreign-body giant cells.

The cellular condition found in the earlier stage gave way to progressive scarring throughout the node. Finally, a dense mass of fibrous tissue remained, in which there were nests of cells, such as have been described. Cellular degeneration took place, and not infrequently regions of necrosis were found. These regions were infiltrated with fibrin, and were surrounded by leukocytes. Cells might undergo fatty degeneration, and hyaline degeneration occasionally took place.

Eosinophils might be uninuclear or polynuclear and were rarely absent. Infiltration by them has attracted much attention; any condition which results in the destruction of lymphocytes will bring about this invasion. The exact relation of these cells to the process has not been determined.

The characteristic cell was large, with clear cytoplasm containing fine reticulum, and the so-called nuclear membrane was distinct. The nucleolus was oval or round, fairly large, centrally situated and stained deeply. In the more rapidly growing cells

many bizarre nucleoli were seen, which stained deeply. Tumor giant cells that usually contained from 2 to 5 nucleoli also accompanied the more malignant types. Germinal centers were necessarily absent, but in earlier cases some still might be present.

Eosinophils, plasma cells, and occasionally foreign-body giant cells occurred, and produced a granulomatous appearance. However, this reaction, accompanied usually by fibrosis and hyalinzation, was a defensive mechanism that varied with the subject, and the degree of malignancy.

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NOTE ON THE SPECTROSCOPIC TEST FOR SULPHEMOGLOBIN

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Within the last few years methods adapted to the use of the hand spectroscope have been developed for demonstrating methemoglobin and sulphemoglobin in blood.[1,2,3] By these methods the presence of the pigments can easily be shown if their concentrations are 1.5 volumes per cent or higher, that is, definite positive results are obtained if 10 per cent or more of the blood pigment exists in an abnormal form. Concentrations below 0.7 volumes per cent are rather difficult to demonstrate by simple methods, particularly if oxalated or citrated blood samples are examined, unless the technician has had considerable experience in such determinations.

Recently a case of cyanosis which was obviously due to poisoning from freshly dyed shoes occured in a nurse in this hospital. We were not able to find any abnormal pigment in the blood, although we felt sure that it was present. This experience led us to attempt to standardize technique to avoid similar errors. It was decided to study the determination of sulphemoglobin because the general importance of this compound seems to be greater than that of methemoglobin, and because the former pigment can be more readily prepared than the latter one. The close resemblance of the two pigments to each other made it seem probable that a method for demonstrating one of them would in general be applicable to the other.

For these experiments large amounts of oxalated blood were pooled and sulphemoglobin was prepared from part of the material by running a current of hydrogen sulfide gas through it for half an hour or more. The excess of hydrogen sulfide was then removed as completely as possible by aeration. Such prepara-

tions gave the characteristic spectrum of sulphemoglobin. They contained, at most, minimum concentrations of free soluble sulphydryl compounds, because negative sodium nitroprusside reactions were obtained when such tests were carried out on the filtrate after the protein was removed with trichloracetic acid. The blood containing sulphemoglobin was mixed with untreated blood in various proportions. Saponin was then added to the samples, and they were allowed to stand for five minutes or more until hemolysis was complete. Next they were centifuged at

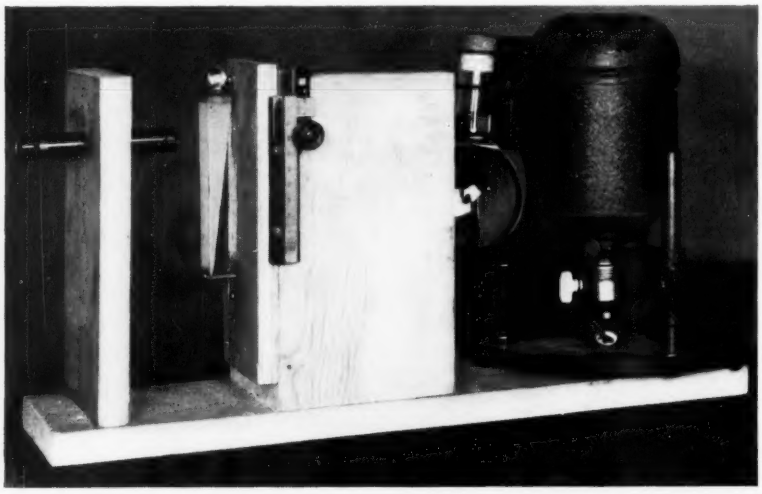

FIG. 1

high speed to remove the excess of saponin and the cell rests. They were then diluted with an equal volume of distilled water and examined with a hand spectroscope in tubes of one-half to three-quarters of an inch in diameter. Results were somewhat more satisfactory when a very bright light equipped with a round-bottomed flask as a condenser was used, but such a system was not necessary except for the detection of very small traces of pigment. The only light which came through the solution was in the red and orange portion of the spectrum, and the characteristic band of sulphemoglobin could be easily distinguished when only 2 per cent

of the hemoglobin was in the altered form, that is, when the concentration of sulphemoglobin (expressed in terms of the unaltered pigment) was 0.3 grams per 100 cc. of blood. By careful comparison with normal blood it was possible to detect amounts approximately half as great as these, but the reading of such concentrations was difficult. When the sulphemoglobin formed was more than 20 per cent of the total pigment its absorption band was so wide that it fused with the general absorption produced by the unaltered hemoglobin. Such solutions, which are easily recognized by their purple-brown color, are either diluted with water, about five parts of water to each part of the diluted, hemolized blood, or are placed in tubes of very small diameter for examination. If the hemolized blood is poured into a conical centrifuge tube it is easily possible to vary the thickness of the layer of solution through which light passes to the spectroscope. This technique not only simplifies the handling of solutions containing large concentrations of pigment, but is useful in studying dilute ones. Such solutions sometimes give very weak absorption bands, and the observer may be in doubt whether a band is present. If the band appears and disappears as the thickness of the solution is varied while the spectrum is under observation, more confidence is felt in the accuracy of the findings.

A convenient apparatus can be arranged for carrying out the examination by using a glass wedge from a Hellige colorimeter, as shown in the illustration. The wedge can be raised and lowered at will by a rack and pinion. If a permanent source of light is used and the slit in the spectroscope always opened to the same extent, the method can be made into a semi-quantitative one. This is done by preparing mixtures of sulphemoglobin and normal blood as described above and noting the lowest scale reading obtained when the band due to the abnormal pigment can be clearly distinguished.

The method described is convenient and delicate. The actual amounts which can be detected vary, of course, with the form of spectroscope used, and are different with different sources of light, but when blood is hemolized with saponin and diluted with an equal volume of distilled water as described, it is hardly possible

to miss significant amounts of pigment. It seems probable, however, that amounts of abnormal pigment which are of little or no clinical significance will sometimes be detected. It seems desirable to emphasize this possibility. Clinical cyanosis should probably not be explained as due to sulphemoglobinemia unless rather large amounts of the pigment (probably more than 1 gram per 100 cc.) are present, or unless all other possible explanations of the condition have been excluded by careful clinical observation and extensive laboratory study.

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SURVEY OF TRAINING SCHOOLS FOR LABORATORY TECHNICIANS*

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This survey represents a systematic attempt to ascertain, if possible, the present status of the so-called "training schools" for laboratory technicians and to assist in formulating an outline of a course of training which may be accepted as a basis for a minimal standard of such a course, exclusive of the courses in Medical Technology offered by universities and colleges of recognized standing. In all, 872 questionnaires were mailed, 376 to members of the American Society of Clinical Pathologists, 401 to superintendents of hospitals approved for interneship by the American Medical Association, of more than 150 beds, 85 to practicing clinical pathologists, not members of the Society and 10 others.

Information was obtained from 399 answers which is considered good and represents a fair cross section view of the training school situation. One hundred sixty-four (43 per cent) members answered, fifty-three (55 per cent) non-members answered and replies were received for 182 (45 per cent) hospitals. In all, 137 laboratories and schools which conduct a course of training for laboratory technicians answered the questions.

Fifty-four of the 164 members, not including members in hospitals, give courses for technicians, twenty-seven, twenty-four medical men and three laymen, of the fifty-three non-members give courses, and fifty-six of the 182 hospitals give courses, ten being conducted by members, forty-four by non-members and two by laymen. In other words of the 188 members heard from

*Part of the Report of the Board of Registry given before the Tenth Annual Convention of the American Society of Clinical Pathologists, Philadelphia, Pennsylvania, June 7–9, 1931.

directly or indirectly, sixty-four (34 per cent) conduct courses for technicians. Of the 150 non-members who are physicians, sixty eight (45 per cent) give courses, while five (71 per cent) of seven laymen also give such courses. Thus, one-third of those replying to the questionnaire are conducting some kind of courses for training laboratory technicians.

Only one-third of the Society's membership and 45 per cent of the non-members responding, are offering a course of training for

TABLE 1

TYPES OF INSTITUTIONS

	NUMBER	PER CENT
Universities and Colleges:		
Organized course in Medical Schools leading to B.S. 4		
Organized postgraduate course leading to M.S. 1		
Organized course in College of Sciences leading to B.S. 2	13	9.5
Unorganized course leading to B.S. 2		
Unorganized postgraduate course 4		
University hospital laboratories	16	12.0
Hospital laboratories	81	59.0
Public Health laboratories	1	1.0
Private laboratories with hospital connection	13	9.5
Private laboratories	5	3.5
Private laboratories conducted by non-medical graduates	3	2.0
Commercial schools	5	3.5

technicians. Of the non-members, there are a number of recognized pathologists, several, members of the American Association of Pathologists and Bacteriologists or teachers of pathology in medical schools, while a few are known to be practicing physicians who are not trained in clinical pathology.

Geographically these courses are offered as follows: Middle west, 48 (35 per cent), East, 48 (35 per cent), South 27 (20 per cent) and West 14 (10 per cent).

Table 1 classifies the replies received from 137 institutions.

Doubtless, there are a number of other universities offering a

course which prepares the candidates as medical technicians but they have no announcement of such a special course nor have they responded to our inquiries. A large number of hospitals, not responding to this questionnaire, and the smaller institutions not included in this survey as well as pathologists who failed to respond are undoubtedly conducting a training course. The number is conservatively estimated to be at least 100.

TABLE 2

SIZE OF HOSPITALS OFFERING COURSES

NUMBER OF BEDS	NUMBER OF HOSPITALS	PER CENT	NUMBER OF BEDS	NUMBER OF HOSPITALS	PER CENT
32–99	10	8	300–399	22	17
100–150	13	10	400–499	15	11
151–199	18	14	500 and more	19	14
200–299	33	25			

TABLE 3

LENGTH OF COURSE

MONTHS	NUMBER COURSES	MONTHS	NUMBER COURSES
2	1	10	2
2	2	12	47
4	2	15	1
5	1	16	3
6	34	18	9
7	1	24	8
8	4	Post graduate	3
9	8	48 (B.S.)	7
		Not given	4

There are several teachers without hospital connections whereas a few pathologists have several hospitals.

Sixty-seven per cent of the hospitals have more than a 200-bed (table 2) capacity.

Twenty-seven per cent of the courses extend for a period of six months while 34 per cent last twelve months. Table 3 gives the summary of the length of courses offered.

High school education is considered sufficient prerequisite by a great majority (64 per cent) of pathologists. The exact requirements are given in table 4.

TABLE 4

PREREQUISITES

	NUMBER	PER CENT
No information or preference	9	6.5
High school	88	64.0
One year college	8	5.5
Two years college	11	8.0
College graduates	11	8.0
Graduate nurse	10	8.0

TABLE 5

STUDENT CAPACITY

STUDENTS	SCHOOLS	STUDENTS		SCHOOLS
1	16	70*		1
2	29	Not given		5
3	17	Universities	6	1
4	17		40	2
5	8		50	2
6	12		65	1
8	6		100	1
9	1		Not given	6
10	1	Commercial schools	24	1
12	3		100	1
15	1		150	1
18	1		Not given	2
26	1			

* This institution may be considered a commercial school.

TABLE 6

INSTRUCTORS*

NUMBER INSTRUCTORS	NUMBER SCHOOLS	NUMBER INSTRUCTORS	NUMBER SCHOOLS
0	2	7	2
1	17	8	2
2	27	10	4
3	20	12	1
4	18	30	1
5	16	Faculty	11
6	7	No information	9

* Ratio of Instructors to Students 1:1.1, exclusive of Universities and commercial schools.

Formal lectures are given in the University and College Course, also, nominally, in the commercial schools. "Lectures" in the majority of the non-teaching hospitals probably mean "informal talks" such as given in any other laboratory. Sixty-nine replied that lectures are regularly given, 15 that some or few are given and 53 that no didactic work is offered.

Fifty-six per cent of the laboratories charge no fees (table 7) while a few charge what is considered an exorbitant fee, as much as or more than the commercial schools. The average fee for forty-three laboratories which charge for the course is $146.00. Including the seventy-seven laboratories which make no charges

TABLE 7

FEES

FEE	NUMBER OF SCHOOLS	FEE	NUMBER OF SCHOOLS
None	77	$125.00	2
$10.00 (Breakage)	2	150.00	6
15.00 (Breakage)	1	180.00	1
25.00	4	200.00	2
50.00 (Breakage)	3	250.00	1
50.00	5	300.00	2
75.00	2	360.00	1
100.00	7	400.00	4
120.00	1	600.00	1

and excluding twelve universities and colleges which charge regular tuition fees, the average fee for the course is about $54.00. Twelve charge the regular University fee. Three did not give information. Board and room was offered as a stipend by one laboratory; small stipends are given by two others.

OUTLINE OF THE SUGGESTED COURSES OF TRAINING FOR LABORATORY TECHNICIANS*

The training of laboratory technicians is, at present, being undertaken by the following institutions: (1) Universities and

*Approved by the Board of Registry of the American Society of Clinical Pathologists as a basis for further study.

colleges, (2) hospital laboratories, (3) Public Health laboratories, (4) private laboratories, and (5) commercial schools.

The first two types of institutions are considered properly adapted for the adequate training of clinical laboratory technicians and the third, for public health laboratorians. Private laboratories are not, as a rule, in a position to undertake such a program while the commercial schools, are, on the whole, considered unacceptable.

The ultimate aim of the Board is to get as many as possible of the universities and colleges to include in their regular curricula a course in Medical Technology either as a four-year course leading to a degree or on a two-year certificate plan. These courses must always be in affiliation with recognized general hospitals where the students shall obtain a part of the practical training as an "interne" or apprentice.

The apprenticeship plan of training in general hospital laboratories under proper supervision is recognized and recommended at the present time for the type of routine and special technicians which constitute the great majority of the present laboratory workers.

UNIVERSITIES AND COLLEGES

The following courses offered, at the present time, are:

(1) In connection with the College of Science, Literature and the Arts, and the Medical School and its hospitals.

(2) In connection with the College of Science, Literature and the Arts with or without the hospital affiliation.

(3) Postgraduate course (a) in various medical sciences, (b) in clinical pathology and medical technology.

(4) Unorganized, elective course.

The curricula recommended are as follows:

(1) A 4-year course leading to the B.S. in Medical Technology. The first two years to be essentially the same as the premedical requirements; the third year, didactic and laboratory studies in basic medical sciences and clinical microscopy and the fourth year, a rotating practical service in the clinical laboratory.

(2) A 2-year course leading to a certificate in Medical Tech-

nology. The first year, didactic and laboratory hours, equivalent to regular college requirement in biology, chemistry, bacteriology and clinical microscopy. The second year, a rotating practical service in the clinical laboratory.

Regular University regulations should govern the personnel, pre-requisites, method of instruction, student capacity, equipment, fees, advertising policy, et cetera. Rotating practical service in the clinical laboratory of the affiliated hospital must constitute an integral part of this course.

Hospital laboratories (apprenticeship plan of instruction)

I. Personnel
   (A) Director, qualified clinical pathologist (or pathologist).
   (B) Medical staff.
   (C) Technical staff, supervising technician and associates, possessing the minimal qualifications defined by the Board of Registry of the American Society of Clinical Pathologists.
   (D) Ratio of instructors to students 1:2 or less, exception, teaching hospitals.

II. Pre-requisites (minimum)
   (A) High school graduation.
   (B) Credits of one-year college chemistry and biology or the equivalent.

III. Length of course (minimum)
   (A) Twelve months of apprenticeship training divided in 2 months (minimum 300 laboratory hours and 40 conference hours) each in the following departments:
      1. Urinalysis
      2. Clinical hematology.
      3. Clinical bacteriology and serology.
      4. Medical chemistry.
      5. Histopathologic technic and metabolism.
      6. Clinical microscopy.

      The above divisions are optional and may be modified.

(B) A longer course of 16, 18 or 24 months with corresponding increase in time spent in each department may be arranged.

(C) Twelve additional months of practical training, supplemented by a course of didactic study is required for specialization or advanced work on any of the above departments.

IV. Method of instruction

(A) Practical training (abundant teaching material must be guaranteed).

1. Personal instruction and demonstration.
2. Practice period.
3. Routine examination (under supervision).

(B) Didactic hours:

1. Required.
   a. Weekly conference.
   b. Quiz hour.
   c. Written examination.
2. Optional.
   a. Medical lectures for nurses.
   b. Series of special lectures.
   c. Autopsies.
   d. Formal series of lectures on basis medical sciences.

V. Student capacity.

The average 100 bed general hospital employing two qualified technicians may enroll two students at a time. Hospitals of less than 100 beds are advised not to conduct a training school.

The Ratio of Instructors to students should be kept at 1:2 or less, in the average non-teaching hospital. Teaching and post graduate hospitals are excepted. Where there are more than six students enrolled at a time, a full time, supervising instructor-technician, besides the regular staff, may profitably be employed.

VI. Equipment, space and location.

Adequate equipment and space to meet the added requirements of training and practice of trainees.

VII. Fees.

A nominal fee (maximum $150.00) for a 12 months course, may be charged. Free instruction under ordinary circumstances, seems unwise. Charging of exorbitant fees on a commercial scale is not justified.

VIII. Advertising.

Commercial advertising should not be necessary. A short announcement in the medical and nursing periodicals may be permissible.

Public health laboratories

These laboratories are considered unadapted for the training of general clinical laboratory technicians. Special technicians and public health laboratorians may adequately be trained by these laboratories. The conditions under which the hospital laboratories should operate are applicable to the public health laboratories in their program of training.

Private laboratories

Private laboratories either directed by a clinical pathologist or operated by a non-medical director, are, as a rule, not adapted for the proper training of technicians. Those, maintaining such a course or school, though not equally obnoxious, must be regarded (with a few exceptions) in the same category as the commercial schools for laboratory technicians. Clinical laboratories of a small hospital (less than 100 bed capacity) are also considered, like the private laboratories, non-adapted for training of technicians. Of course, there are exceptions among these institutions.

Commercial schools

No attempt is being made, at this time, to regulate or standardize the existing curricula of these schools. As a rule, they are being operated by commercially minded promotors or direc-

tors, in the name of education and medical science. The objections against these schools are fundamental. They represent all that is contrary to the principles which the medical profession holds sacred and ethical. The commercial character of these institutions is clearly indicated by their advertising policy, the teaching facilities and personnel, the tuition they charge, the type of students they enroll, et cetera. They often advertise extensively in lay journals in exaggerated and misleading terms.

Teaching facilities are usually inadequate, more students being enrolled than can be properly accommodated either from the standpoint of the available space and equipment or from that of the teaching personnel. Teaching material is sorely inadequate both in number and variety of the specimens. Contact with the sick, representing various types of disease, is entirely lacking. The teaching force consists often of poorly trained technician with little or no teaching or technical experience. Educational prerequisites of the applicants are often disregarded in order to increase the enrollment. The tuition and incidental expenses are unusually high considering the kind of training they offer. A large majority of the "graduates" would be found lacking in qualifications essential in a properly trained technician.

Therefore, until these schools shall be directed by a clinical pathologist of high professional standing, are conducted on the sound educational basis with a staff of qualified teachers in sciences and a close affiliation with one or more general hospitals, and shall eliminate such objectionable features as extensive commercial advertising and propaganda and exorbitantly high rates of tuition, it would be useless to make any attempt to standardize the curricula of these institutions. It may safely be predicted that when the standardization of the courses of training for technicians offered by the recognized colleges and hospitals is accomplished, coupled with the awakening of the medical profession to the true character of these schools, the commercial institutions offering a course for laboratory technicians may cease to be the serious problem which they are now.

EDITORIAL

The Relation of Clinical Pathologists to the Cancer Problem*

The American Society of Clinical Pathologists has had a short but honorable career, honorable because it has proved that its sole purpose is not to create offices to be filled but rather to carry on a profitable constructive program. Its coöperation with the American College of Surgeons in the past has been much appreciated. The nomenclature adopted by the Registry of bone sarcoma was arrived at after consultation between Fellows of the College and a committee of this organization.

To the individual members of this Society the College owes much on account of their close coöperation with our Department of Hospital Activities in its program of hospital standardization.

A clinical pathologist is an individual that it is a bit difficult to define, and the term bears a different significance in different parts of the country. It is indeed fortunate that the individual who carries on the laboratory work in the hospital has not allowed his activities to be circumscribed by any limited definition of his position. There is a tendency in some of the specialties of medical art and science to circumscribe rather too closely one's interests to the detriment of the specialty which is being practised. Fortunately this is not so with the clinical pathologist whose interests are all-embracing, or should be. We must remember that the dictionary still defines the pathologist as "one skilled in the science treating of diseases, their nature, causes, progress, results, et cetera." This definition sufficiently indicates the breadth of scope of the clinical pathologist's activities.

* Read before the Annual Banquet of the Tenth Annual Convention of the American Society of Clinical Pathologists, Philadelphia, Pennsylvania, June 7–9, 1931.

Within the very recent past specialization has grown up to a remarkable extent within the confines of what may be defined as pathology. We have bacteriologists, animal parasitologists, mycologists, immunologists, biochemists, epidemiologists, and so on almost *ad infinitum*, and each of these sciences now has enough sub-divisions to make the meticulous systematist tremble for the accuracy of his premises. If we might imitate the methods of the systematist, the pathologist now merits the dignity of an order —say, Knight Commander of the Laboratory. A member of this order in one direct line only might be indicated as follows:

Family—*Zoologist*
Tribe—*Parasitologist*
Genus—*Helminthologist*
Species—*Trematode immunologist*

and so this method might be elaborated to form a wide-spreading and comprehensive phylogenetic tree.

In my early days in the laboratory I did gross and microscopic pathologic anatomy and made some crude chemical and microscopic examinations of the body fluids. However, in the early days I did no Wassermann, Kolmer, or Kahn tests. I searched for no pathogenic treponema; rarely did a spinal fluid count; allergic and anaphylactic phenomena were not within my ken; pneumococci were not typed, vaccines were in their infancy, my laboratory was not cluttered up with colorimeters; basal metabolism was not a clinical test; the electrocardiograph was unknown; the endoscopist did not pester me with submicroscopic specimens; T. A. T. meant no more than the letters spell; pH meant nothing to me; the bi-polar theory of vital phenomena was still aborning in Cleveland; and so I could go on enumerating the advances in knowledge that have been made during my own medical career. Within the sphere of pathology I was a jack of all trades and worked for sixteen to eighteen hours a day but the majority of the activities of the present day clinical laboratory were unknown and unthought of. Still, I must admit that people were ill, some died, some recovered, and the accuracy of the diagnoses was not small.

You will see to what I am leading when I say that this is a day of minute specialization and that any man to know his subject well must have a wealth of experience in his own line. No longer can a country doctor with a Bunsen burner and a test tube for his laboratory equipment make the additions to knowledge that he once could. Nor can a man who has had a few months of laboratory training in a general hospital be an expert in all of the sciences whose fringes he must touch. What has all this to do with the clinical pathologist and his relation to cancer?

The American College of Surgeons through its Committee on the Treatment of Malignant Diseases has recently evolved a minimum standard for cancer clinics in general hospitals, which is as follows:

1. Organization. There shall be a definite organization of the service, and it shall include an executive officer and representatives of all the departments of the hospital which are concerned in the diagnosis and treatment of cancer. The services of a secretary and of a social service worker shall be available.

2. Conferences. As an essential feature of the service there shall be regular conferences or consultations at which the diagnosis and treatment of the individual cases are discussed by all members of the clinic who are concerned with the case.

3. Patients. Reference to the cancer clinic of all patients in whom the diagnosis or treatment of cancer is to be considered shall be either voluntary or obligatory in accordance with the vote of the medical staff or of the governing board of the hospital.

4. Equipment. In addition to the diagnostic and therapeutic surgical equipment which is required in every approved general hospital there shall be available an apparatus for x-ray therapy of an effectiveness which is generally agreed upon as adequate, and an amount of radium sufficient to insure effective treatment.

5. Records. In addition to the records which are required in every approved general hospital, there shall be additional records of: (*a*) The details of the history and of the examination for cancer in different regions of the body, such as are indicated on the form records which are recommended by the Committee on the Treatment of Malignant Diseases, American College of Surgeons. (*b*) The details of the treatment by radium or x-ray as indicated on the form records which are recommended by the Committee on the Treatment of Malignant Diseases, American College of Surgeons. (*c*) Periodic examinations at intervals for a period of at least five years following treatment.

6. Treatment. The treatment of cancer patients shall be entrusted to the members of the staff of the cancer clinic except in cases in which adequate treat-

ment in accordance with the collective recommendation of the staff of the cancer clinic can be procured otherwise.

This standard has just been published with an elaboration of its various clauses. I hope that you will all agree with me that it is fundamental. The underlying principles on which these recommendations are based may be stated in the form of four axioms:

1. The diagnosis and treatment of cancer is no longer a one man job.
2. The cancer patient merits the advantage of the best available medical knowledge.
3. The general practitioner who cannot be versed in all of the ancillary sciences should have made available to him the facilities and knowledge possessed by those versed in these sciences.
4. Immediate and complete records of all cases are necessary in order that trustworthy conclusions may be drawn as to the value of treatment administered.

It is difficult to forecast what the future organization of medical practice will be, and this is rather aside from our point but it seems obvious that the type of group practice which I am here defining is a necessary essential to medical progress. It takes nothing from the general practitioner but offers to him a service which at the present is available to relatively few and those chiefly in the larger medical centers.

In this standard emphasis is placed upon the coöperation of the surgeon, the radiologist and the clinical pathologist in arriving at a decision as to the diagnosis, prognosis and treatment of individual cases. This coöperation is essential for success and every medical organization must take cognizance of it.

The pathologist must equip himself specially to carry on this work in tumor pathology. There is rapidly coming into existence another specialty within a specialty. The expert tumor pathologist must know not only how to make a tissue diagnosis as to the cellular elements constituting the tumor under discussion but he should also know the natural course of such a tumor as it develops in different parts of the body. He must know its grade of malignancy. He must know its radiosensitivity. He must

be in a position to advise with the clinician and the radiologist as to the most effective method of treatment of the particular tumor under discussion. Such knowledge can only be gained by familiarity with a large group of patients.

Perhaps I can illustrate this well by saying that the preëminent position which Dr. James Ewing occupies among the tumor pathologists of this country is due in large part not to any of his academic attainments but rather to a careful personal scrutiny and analysis of large groups of tumor patients not only from the standpoint of the microscopic changes in the tissue but from the clinical and radiological standpoints. He has profitably associated himself with the clinicians and with the radiologists and has fortified himself with a knowledge of the subject of tumors from as many different angles as possible.

I do not wish to be held responsible for introducing more specialties and a greater confusion into the already almost indissolubly intricate maze of medical practice but I do wish to be considered among those who are working to bring the best available medical knowledge of the present day to bear on every individual cancer patient throughout the country. I recognize the value of cancer institutes and cancer hospitals, but I also recognize that economic conditions are such that the most practical means at present available of bringing the best of medicine to each of the quarter of a million of cancer patients throughout this country is by the utilization of already existing general hospitals. I have welcomed this opportunity of bringing this subject to your attention and I look for much assistance from you in putting this program into effect.

B. C. Crowell.

SOCIETY NEWS AND NOTICES

Constitution and By-Laws on the American Society of Clinical Pathologists

CONSTITUTION

Article I—Name

This Organization shall be known as the American Society of Clinical Pathologists.

Article II—Objects

The objects of this society shall be: (a) To promote the practice of scientific medicine by a wider application of clinical laboratory methods to the diagnosis of disease; (b) to stimulate original research in all branches of clinical laboratory work; (c) to establish from time to time standards for the performance of various laboratory examinations; (d) to elevate the scientific and professional status of those specializing in this branch of medicine; (e) to encourage a closer co-operation between the practitioner and the clinical pathologist.

Article III—Membership

Section 1. The membership of this society shall consist of (a) Fellows, (b) associate, (c) honorary, and (d) corresponding members.

Section 2. Fellows shall be graduates in medicine from a recognized medical school, who have specialized in clinical pathology for at least three years and who are devoting a major portion of their time to this field.

Section 3. Associate Members shall be graduates of recognized scientific institutions who have made such contributions to any of the sciences relating to clinical pathology and whose membership will so further the objects of the Society as to make them eligible for associate membership. Associate members shall pay the regular dues and have all the privileges of Fellows except those of voting and holding office.

Section 4. Honorary members shall have distinguished themselves by research or personal sacrifice in the cause of scientific medicine to warrant their recommendation for election by the Board of Censors. They shall have all the privileges of active members except that of voting and holding office. They shall be exempt from paying dues.

Section 5. Corresponding members shall be residents of foreign countries in good ethical standing who have distinguished themselves in any of the branches of clinical pathology. They shall be exempt from paying dues.

Article IV—Officers

SECTION 1. The officers of this society shall consist of a President, President-Elect, Vice-President, Secretary-Treasurer, Executive Committee, Board of Censors, and Board of Registry of Technicians.

SECTION 2. Officers shall be elected by a majority of the ballots cast at the annual executive business session.

SECTION 3. The Executive Committee shall be composed of six Fellows of the Society, who shall each hold office for three years or until their successors are elected; two to be elected annually.

SECTION 4. The Board of Censors shall be composed of six Fellows of the Society, who shall each hold office for three years or until their successors are elected; two to be elected annually.

SECTION 5. The Board of Registry of Technicians shall be composed of six Fellows of the Society, who shall each hold office for three years or until their successors are elected; two to be elected annually. The first Board shall consist of six Fellows, two of whom shall be elected for a term of one year, two for a term of two years, and two for a term of three years. It shall elect its own Chairman from among the holdover members and Secretary-Treasurer.

SECTION 6. Vacancies in the interim on the Executive Committee, Board of Censors, or the Board of Registry of Technicians shall be filled by appointment by the President.

Article V—Duties of Officers

SECTION 1. The President shall preside at all meetings of the Society, be an ex-officio member of all committees and perform all other duties that devolve on him by custom and parliamentary usage.

SECTION 2. In the absence of the President, the President-Elect, and in the absence of both, the Vice-President shall perform the duties of the President.

SECTION 3. The Secretary-Treasurer shall keep a correct and permanent record of the meetings and the transactions of the Society. He shall provide a copy of this record for all members in good standing, conduct the correspondence and perform such other duties as customarily pertain to the office of Secretary. He shall receive and keep funds of the Society and pay out of the same with consent of the Chairman of the Executive Committee. He shall give bond satisfactory to the Executive Committee, the cost of which shall be borne by the Society. He shall make a complete financial report at the annual meeting of the Society. He shall serve a term of three years.

SECTION 4. The Executive Committee shall audit the Treasurer's account annually or as often as they deem necessary. The Chairman shall hold the Treasurer's bond. The Executive Committee shal have general supervision of the financial affairs of the Society.

SECTION 5. The Board of Censors shall investigate all applications for membership and submit their recommendations at the annual meeting of the

Society. They shall receive and consider all complaints concerning the conduct of members and present a report at the executive session, with their recommendations. Suspension or expulsion from membership in the Society shall be by three-fourths vote of those members present and voting at a regular executive session.

SECTION 6. The Board of Registry of Technicians shall conduct a Registry of Technicians, receive applications for such, pass on their qualifications and issue certificates to those meeting the requirements. They shall investigate schools for the training of technicians, registering those approved. They shall conduct a placement bureau for technicians.

Article VI—Amendments

This Constitution may be altered or amended by a vote of three-fourths of the Fellows voting at a regular meeting in executive session, provided said alteration or amendment had been submitted to the membership by publication or otherwise at least thirty days prior to the annual meeting.

BY-LAWS

Article I—Applications for Membership

Application for membership shall be made on a form authorized by the Society, signed by the applicant, recommended by two members, approved by the local Counselor and the Board of Censors. At least thirty days prior to the convention, the Secretary shall send a list of applicants to every member of the Society.

Article II—Qualification for Membership

SECTION 1. Fellows shall be graduates in medicine from a recognized medical school, who have specialized in clinical pathology for at least three years and who devote the major portion of their time to this branch of medicine. They must be members in good standing of their local and state society.

SECTION 2. Applicants for Fellowship, associate, and corresponding membership approved by the Board of Censors, shall be elected by a ballot of three-fourths of the Fellows voting at any regular meeting.

SECTION 3. Honorary members shall be recommended by the Board of Censors, and elected as in Section 2.

Article III—Dues

SECTION 1. All Fellows and Associate Members shall subscribe to this constitution at the time of their election to membership and shall pay an initiation fee of Twenty-Five Dollars ($25.00), payable with application for membership.

SECTION 2. The annual dues for Fellows and Associate Members shall be Ten Dollars ($10.00), payable December first for the following year, and if unpaid on January first the subscription for the Official Journal will lapse. Five

Dollars of the annual dues shall be used as subscription for the Official Journal. New members elected at the annual meeting shall pay dues for the current year of Five Dollars ($5.00) to cover the subscription of the entire volume of the Official Journal for that year.

SECTION 3. Members in arrears for dues for sixty days shall be notified thereof by the Secretary-Treasurer by means of a "return receipt" registered letter. Members in arrears for dues for ninety days shall be automatically dropped from the roll for non-payment of dues. Members may be reinstated upon payment of all arrears and current dues within one year without recommendation by the Board of Censors.

Article IV—Committees

SECTION 1. A Board of Counselors shall be appointed by the President. They shall represent such districts as may be determined. It shall be the duty of the counselors to act in the interest of the organization in their respective communities.

SECTION 2. A Nominating Committee of three shall be appointed by the President at the opening of the convention, whose duty it shall be to prepare a list of nominees for the various offices for balloting by the Society. Additional nominations may be made from the floor.

SECTION 3. The President shall appoint a Program Committee consisting of three Fellows, the Chairman of which shall be the Secretary of the Society, whose duty it shall be to arrange the scientific program for the annual meeting.

SECTION 4. The President shall appoint a Committee of Exhibits, of which the Secretary of the Society shall be a member whose duty it shall be to arrange for scientific and commercial exhibits at the annual meeting.

SECTION 5. The President shall appoint a Publication Committee.

SECTION 6. The President shall appoint a Research Committee.

SECTION 7. The Executive Committee shall appoint an Editor for the Official Journal of the Society for a term of three years. The Editor so selected together with the President of the Society and the Chairman of the Executive Committee of the same shall appoint an Advisory Editorial Board for a period of three years. The duties of this Advisory Editorial Board shall be to foster and supervise all official publications of the Society. The three year term of office of the first Board so appointed shall expire on January first 1934. Nothing in this Section shall prevent continuing a Publication Committee which has not yet discharged its duties.

Articles V—Quorum

Twenty-five Fellows shall constitute a quorum.

Article VI—Meeting Place

SECTION 1. The time and place of the annual meeting and other meetings of the Society shall be determined by the Executive Committee, notice of which shall be mailed to every member at least thirty days prior to such meetings.

Article VII—Elections

SECTION 1. The Society shall elect annually by ballot at an executive session held on the last day of the annual meeting the following officers: President-Elect, Vice-President, Secretary-Treasurer, two Fellows to fill vacancies on the Executive Committee, two Fellows to fill vacancies on the Board of Censors, and two Fellows to fill vacancies on the Board of Registry of Technicians.

SECTION 2. The President-Elect and newly-elected officers shall be inducted into office at the conclusion of the meeting.

Article VIII—Code of Ethics

SECTION 1. The Code of Ethics of this Society shall be the same as that of the American Medical Association.

SECTION 2. It shall be deemed unethical for members to publish objectionable laboratory advertisements in any form whatsoever. The Board of Censors to act as judges in the matter, the members having privilege of appeal to the Society at a regular executive session.

SECTION 3. It shall be considered unethical for a member to lend his name for publication in any laboratory advertisement or announcement, which violates the Code of Ethics. The borrowing of names of other physicians, scientists or laymen, on the basis of an occasional service or consultation, for purposes of advertising or to sanction the work of a laboratory is misleading and unethical.

SECTION 4. Any system of secretly dividing or rebating fees for laboratory services shall be considered unethical.

Article IX—Standing Rules

SECTION 1. The Chairman, at all regular annual meetings, shall first call the members assembled to order in executive session for the purpose of transacting such business and appointing such committees as are herein required, together with the making of other arrangements consistent with conducting the annual meeting.

SECTION 2. Scientific papers limited to twenty minutes for members, thirty minutes for guests, longer only on consent of the majority.

SECTION 3. Opening discussion limited to ten minutes, all succeeding discussions five minutes except by consent of the majority.

SECTION 4. Members desiring to speak twice must obtain consent.

SECTION 5. Non-members can be given the privilege of the floor only by consent.

SECTION 6. A paper read before this Society becomes the property of the Society, to be published in the Official Journal provided it meets the approval of the Advisory Editorial Board, except that the privilege for prior publication may be granted by the Editor.

SECTION 7. Order of Business for Executive Session:

1. Call to order.
2. Reading of Minutes.
3. Unfinished business.
4. Reports of committees.
5. Election of members.
6. New business.
7. Nominations.
8. Election of officers.
9. Induction of officers.
10. Adjournment.

Article X—Parliamentary Procedure

All parliamentary proceedings at the meetings of this Society shall be governed by Roberts' Rules of Order, except where otherwise provided.

Article XI—Amendments

Amendments of these by-laws must be submitted in writing at the opening of the annual meeting and may be voted upon at the executive business session.

The attention of the Society is called to the following changes in the By-Laws: Article III, Section 2 relates to the subscription to the JOURNAL and specifies that $5.00 of the annual dues shall be used for such subscription for each member. The Section also covers the cost of the JOURNAL to new members.

Section 3 of the same Article, refers to the change in the method of notifying members in arrears for dues.

Article IV, Section 3 provides that the Secretary shall be Chairman of the Program Committee. Section 4 of the same Article provides that the Secretary shall be Chairman of the Committee on Exhibits. Section 7 is an addition providing for the Editor and Editorial Board of the official JOURNAL of the Society.

Article IX, Section 6 has been slightly changed to provide for the approval of papers by the Advisory Editorial Board before their publication in the JOURNAL.

The Secretary announces the following Committees appointed by the President:

Research Committee

ALVIN G. FOORD, *Chairman*
ERNEST SCOTT
M. PINSON NEAL

Necrology Committee

HARRIET J. LAWRENCE, *Chairman*
W. G. GAMBLE
HERBERT R. MILLS

Program Committee

A. S. GIORDANO, *Chairman*
ALBERT H. BRADAN
C. E. RODERICK
HERMAN SPITZ

Public Relations Committee

B. W. RHAMY, *Chairman*
F. B. JOHNSON
G. S. GRAHAM
J. J. MOORE

Vaccine Therapy Committee

R. A. KEILTY, *Chairman*
JOHN A. KOLMER
JOHN EIMAN
A. B. HUNTER
B. E. STOUT
J. H. BLACK
RUTH GILBERT

The Chairman of the Program Committee, Dr. A. S. Giordano, is ready to receive titles from those desiring to present papers at the next annual meeting which will be held on May 6–9, 1932 at New Orleans, Louisiana.

The Research Committee after due deliberation and consultation with officers in the Society has decided on the following subjects for research activities of the Society for the coming year. Some of the problems or subjects may not appeal to all the members, but at the same time they should be of interest to most of the members engaged in hospital diagnostic work. Hematologic material is stressed at this time because of the simplicity of recording and compiling. In later years more involved studies can be taken up.

1. The hematologic registry will be continued and a summary of the cases will be presented at the next meeting of the Society. Reports are desired on acute leukemia, acute mononucleosis, agranulocytic angina, and blood dyscrasis following treatment by the arsphenamines, and cases showing a blood picture resembling pernicious anemia, but in which a definite etiology is proved. All the records and slides of these cases will be on file and when sufficient numbers are on hand they will be loaned to the various members of the Society on request. Cases should have a good history, complete blood counts, and blood smears, perferably at intervals, and slides of bone marrow, lymph nodes, spleen or

other organs of interest. Questionnaires for cases of acute leukemia and agranulocytic angina will be sent from the Secretary's office; other cases can be reported without a questionnaire. Please ferret out recent cases and send them as soon as possible to the Chairman of the Committee.

2. It is also recommended that each member who meets with a case of hemophilia, thoroughly study the case by appropriate laboratory tests including clotting time of venous blood and prothrombin time, simultaneously with a normal control, and try the effect of subcutaneous injection of ovarian extract as reported by Carroll Birch (Proc. Soc. Exp. Biol. & Med., April, 1931, page 752, and Jour. Am. Med. Assn., July 25, 1931). Birch's results warrant a widespread trial of the method, and only by the pooling of the results of a large number of cases can a reasonable impression of the efficacy of the treatment be determined.

3. Reports are also desired of the blood findings in cases of broad tapeworm infestation. Ordway's questionnaire to a limited number revealed practically no cases of blood changes. Please give a short synopsis of case with laboratory record and blood smears if any have been kept.

4. Because of the paucity of follow-up records of cases of splenectomy for thrombocytopenic purpura the Committee recommends reporting all cases at this time. By doing so information of several hundred cases would be available for study by any one desiring to use the loan collection. Please send history, laboratory records and blood smears and sections of the spleen if available, but if no slides are on hand do not neglect to send in the case record without them. Recent or old proved cases are satisfactory.

5. The Committee recommends keeping records of the results of the Friedman urine test for pregnancy, using the rabbit as recommended by Reinhart and Scott (Am. Jour. Clin. Path., February, 1931). Just before the meeting in New Orleans the data will be collected. Especially should tests be done in cases of chorioepithelioma, suspected abortion or abdominal pregnancy, most of which occur too rarely in any one hospital for collection of any large series.

6. Finally, the Committee recommends culturing the blood in cases of chronic rheumatoid arthritis according to the method used by Cecil, et al., (Jour. Exp. Med. Nov. 1, 1929). Cecil's findings of more than 60 per cent positive *Streptococcus hemolyticus* cultures (Jour. Am. Med. Sciences, Jan. 1931, page 12) have been corroborated by one of our members, Gray (Jour. Med. Soc. of New Jersey, Jan. 1931, page 38). No doubt many of our men have been asked to try Cecil's method. By pooling results it can be established whether or not the method is satisfactory for general use. Possibly this work will link in well with the activities of the Vaccine Therapy Committee.

It is hoped that all the members will feel that the cases reported to the registry can be used in other publications. The registry will merely file them and keep them on record for the benefit of the Society members who wish to go over the material. No one member sees enough of the conditions mentioned above to know the whole story of the diseases. As evidence of this it is interesting to note that some of the cases reported as agranulocytic angina two years ago were really acute leukemias. Many members have in their files a case or two or more of the above conditions, but not enough to furnish material for a paper. These cases are practically buried but can be used if properly collected. Start sending material as soon as possible and do not wait until just before the meeting, for the Committee must have time to go over the material. A short resumé of a case is satisfactory but nothing surpasses a well-written one or two page case report. Please see that all pertinent blood examinations are made on all cases, repeatedly if possible. Remember the registry is yours and will be only as interesting as you make it.

Please send material to the Chairman of the Research Committee.

A. G. Foord, *Chairman,*
Pasadena Hospital,
Pasadena, California.

A communication has been received from the Italian journal, Diagnostica e Tecnica di Laboratorio, to the effect that members

of the American Society of Clinical Pathology are entitled to receive the journal at the reduced price of 75 lire (about $4.00). The journal is published at Naples, Piazza S. Domenico Meggiore, 9.

American Journal of Clinical Pathology

Manuscripts and books for review should be sent to Dr. Thomas B. Magath, Mayo Clinic, Rochester, Minnesota. Manuscripts must be typewritten and all figures and tables should be in such form as to be ready for the printer. The expense for a limited number of cuts can be borne by the Society; expense for cuts in excess of this number will have to be defrayed by the author. The nomenclature for species of bacteria will be that given in Bergey's "Manual of Determinative Bacteriology." Bibliographic references will be limited to the papers actually referred to in the text. Such citations must be arranged in alphabetic sequence and made in the following form: author's name followed by initials, title, journal, volume, inclusive pages, date.

(Examples) Kolmer, J. A.: Toxin production by *Spirochaeta pallida*. Arch. Derm. and Syph., 20: 180-190, 1929.

McFarland, Joseph: A text-book upon the pathogenic bacteria and protozoa for students of medicine and physicians. Philadelphia and London: W. B. Saunders Company, 1919, pp. 858.

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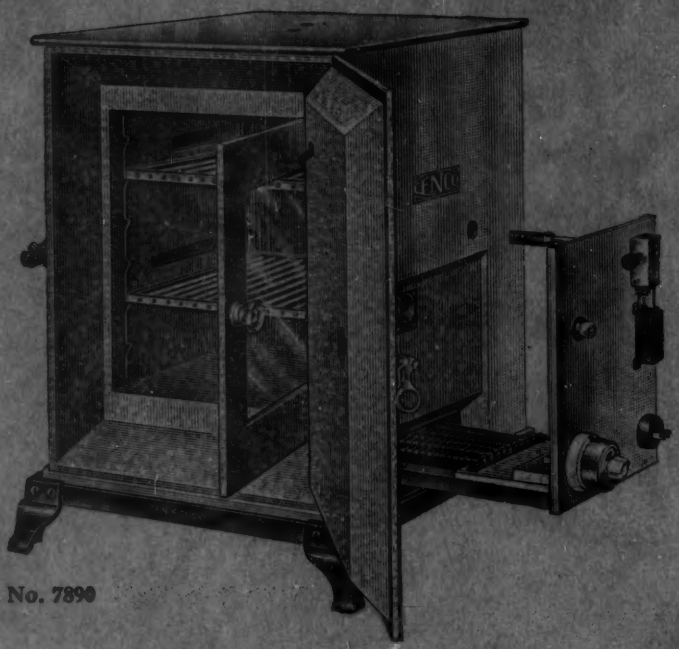

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